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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/641,471	08/18/2000	Carol M. Kinoshita	10278-017001	6615

26161 7590 12/29/2005

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/641,471	KINOSHITA ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *105,106,109-131,133-142,144-164,167-171,184 and 185* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *105,106,109-131,133-142,144-164,167-171,184 and 185* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment field September 26, 2005 amending claims 141, 142, 167 and 168 has been entered.

Claims 105, 106, 109-131, 133-142, 144-164, 167-171, 184 and 185 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 141 and 142 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 141 and 142 depend from claim 139 drawn to a method of use of a class I mannosidase inhibitor. By definition, class I mannosidase inhibitor inhibits mannosidase I. Mannosidase I is an enzyme that cleaves α1,2 linkages not α1,3 linkages or α1,6 linkages. Thus, class I mannosidase inhibitor prevents the removal of α1,2 mannose residues as a result of mannosidase I substrate specificity. Claims 141 and 142 recite the limitation "wherein the mannosidase inhibitor further prevents the removal of one" "α1,3 mannose residue" or "α1,6 mannose residue", respectively. While some specific mannosidase I inhibitors such as kifunensine and 1-deoxymannojirimycin may in addition weakly inhibit mannosidase II and consequently prevent the removal of α1,3

mannose residues or α1,6 mannose residue, the claims are not limited to said specific inhibitors (Shah et al. Biochemistry, 2003, Vol. 42, pages 13812-13816). Therefore, it is unclear how the inhibitor of mannosidase I can prevent removal of residues on which mannosidase I does not act.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 105, 106, 109-128, 130, 131, 133-138, 184 and 185 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedman et al. in view of Smith et al.

Friedman et al. (US Patent 5,549,892, form P7-0-1449 filed November 30, 2000, reference AD) teach the importance of a glycoprotein, human GCB, needed for treatment of Gaucher's disease. They teach the importance of GCB remodeling for the production of a pharmaceutically effective preparation and the production of a remodeled recombinant human GCB in CHO cells. The sequence encoding human GCB comprises exogenous regulatory and coding sequences (columns 3, 4). Friedman et al. teach that the remodeling of the carbohydrate chains may be accomplished by

several different alternative ways such as utilizing mutant cell lines deficient in certain carbohydrate synthetic pathways (column 6, lines 1-15).

Smith et al. (US Patent 5,939,279) teach that growing eukaryotic cells in the presence of inhibitors of glycoprotein processing can alter N-linked oligosaccharides. They teach that two such inhibitors, deoxymannojirimycin and kifunensine, inhibit α-1, 2 mannosidases that trim mannoses from $Man_9(GlcAc)_2$ (column 8, lines 4-15). They teach the method of preparing high mannose $Man_9(GlcAc)_2$ glycoproteins by treating human HT-29 cells with mannosidase I inhibitors, deoxymannojirimycin or kifunensine (columns 7-8, column 9, claim 8). With regard to claims 109 and 110, Smith et al. teach the required range of the kifunensine concentration (column 8, lines 24 and 25). With regard to claims 111-114, Smith et al. teach the required range of the swainsonine concentration (column 8, line 26). Therefore, *Smith et al. teach a general method of altering oligosaccharides attached to protein moiety in glycoproteins by growing human cells in the presence of inhibitors of glycoprotein processing*. They teach that the treatment of human HT-29 cells with kifunensine results in glycoproteins comprising $Man_9(GlcAc)_2$. One of such glycoproteins present in HT-29 cells is GCB.

Therefore, at the time the invention was made, the importance of remodeling GCB to produce hmGCB has been acknowledged. Remodeling by growing eukaryotic cells in the presence of inhibitors of glycoprotein processing has been known. The use of mannosidase inhibitors, such as kifunensine, as a tool for such remodeling to obtain $Man_9(GlcAc)_2$ oligosaccharide was known. The genetic manipulation of protein

expression and techniques to make a knockout gene of a known structure and antisense molecule therefor were known.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to grow cells that whether recombinantly or naturally express GCB in the presence of mannosidase inhibitors in order to prepare hmGCB. Any human cell such as HT-29, for example, or a mammalian cell transformed with a DNA encoding human GCB such as CHO as taught by Friedman et al. or COS, can be employed.

One of ordinary skill in the ad at the time the invention was made would have been motivated to specifically purify GCB in view of its pharmaceutical importance taught by Friedman et al. The high expectation of success is provided by Smith et al. who teach the requisite step for preparing remodeled glycoproteins. The purification of proteins from the cells is standard in the art and is taught by Friedman et al., for example.

Claims 129, 139-142, 144-164 and 167-171 are rejected under 35 U.S.C. 103(a) as being unpatentable over Treco et al. in view of Smith et al. and further in view of Friedman et al.

The teachings of Friedman et al and Smith et al are outlined above.

Treco et al (US Patent 6,270,989) teach that in many cases, it is desirable to produce human therapeutic proteins in human cell, for example, when it is desired that the glycosylation pattern of the protein be similar to patterns normally found on human cells (column 3, lines 6-15). They teach the production of a pharmaceutically useful

preparations of various proteins using gene activated endogenous genes encoding said proteins (abstract). They teach various human cells that can be used for the production of the endogenous proteins (e.g., claim 97). They teach the production of GCB (gene-activated GCB) using HT1080 cells (claims 324, 332).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to grow human cells producing GCB in the presence of mannosidase inhibitors in order to generate hmGCB. It would have been further obvious to use human cells producing GA-GCB because they produce a greater amount of the desired protein as compared to the cells before gene activation.

Friedman provides motivation for the production a pharmaceutically effective preparation of a human GCB wherein its carbohydrate chains are remodeled. Smith provides tools to obtain the desired carbohydrate structure by growing the cells expressing GCB in presence of mannosidase inhibitors.

Response to Arguments

Applicant's arguments filed September 26, 2005 have been fully considered but they are not persuasive.

With regard to the 103(a) rejection, Applicants argue that "Friedman et al. explicitly teach away from preparations of GCB that have the requisite carbohydrate structure. Friedman et al. discuss the remodeling of GCB obtained from placenta (pGCB) and recombinantly produced GCB (rGCB)[1]. (It should be noted that treatment to remove other sugars to expose mannose residues as disclosed by Friedman is not the

same as a treatment with a class I mannosidase inhibitor to prevent removal of mannose residues from a precursor oligosaccharide). Throughout the Friedman reference, the "surprisingly" improved pharmacokinetics of remodeled rGCB as compared to remodeled pGCB are reported. See, e.g., column 4, lines 27-45 of Friedman et al. which states

> it was unexpectedly discovered (FIG. 2) that remodelled p-GCR and remodelled r-GCR have different cell type distributions in vivo although the blood clearance of both r-GCR and p-GCR is comparable. Approximately twice as much r-GCR targets Kupffer cells than does p-GCR. This difference was observed at every time point analyzed (FIG. 2). Table 1 shows that this effect is batch independent. Two batches of r-GCR (batch 1 199 and batch 1 167) were administered to mice according to the protocol in Example 2 and the animals sacrificed 0.33 hours after administration. The percentage of r-GCR retained in Kupffer cells was found to be twice that of p-GCR. (emphasis added)" (Remarks, pages 14-15).

Applicants further argue that "Thus, Friedman et al. specifically attribute the reduced pharmacokinetics of pGCB to the presence of a high mannose chain that is not present in rGCB. Since Friedman explicitly teach that the presence of high mannose oligosaccharides contribute to the reduced pharmacokinetics of p-GCB, a skilled artisan would clearly not be motivated by this reference to utilize the claimed method that results in an increase in high mannose structures on GCB" (page 15). These arguments are not persuasive because Friedman does not attribute the reduced pharmacokinetics to the differences in carbohydrate structures. Friedman just considers them along with other reasons such as the differences in the amino acid sequences between pGCR and rGCR (US 5,549,892, column 4, lines 61-67). These arguments are not persuasive because at the time the invention was made glucocerebrosidase was one of the most expensive enzymes among drugs. This was mostly due to the cost of remodeling. The

targeting ability is not the only aspect of the invention that should be considered. Therefore, one of ordinary skill in the art would have been motivated to produce glucocerebrosidase cheaper, even if the resulting product has targeting ability at the acceptable level albeit decreased. Obviously, to remodel glucocerebrosidase using the cell producing it is significantly cheaper than to remodel the carbohydrate structure of the purified glucocerebrosidase using a multistep process. Friedman teaches that the approach used in the patent is one among other possibilities that could lead to the same product whereas said product may have some variations in targeting ability.

Applicants further argue that Smith "has absolutely nothing to do with modifications of proteins to increase their uptake by cells expressing mannose receptors. Smith et al. teach that gram-negative bacteria bind to high-mannose oligosaccharides on host cell surfaces. This is completely unrelated and irrelevant to the subject matter of the claims" (pages 16-17). This is not persuasive because Smith teaches the method of obtaining the glycoprotein comprising the desired oligosaccharide such as $Man_9(GlcAc)_2$ by growing human cells in the presence of mannosidase inhibitors. GCB is present in these cells and therefore, is among the proteins comprising said oligosaccharide moiety. Friedman et al teach that carbohydrate chains of GCB should be altered in order for GCB to be therapeutically effective. Smith provides a method for the desired remodeling. Neither of the references teaches the same invention as the claimed by Applicants. However, as the references in the 103(a) rejection, these references do not have to disclose the same invention but only to make it obvious.

Applicants further argue that "Treco et al. do not mention carbohydrate modification, mannosidases, or mannosidase inhibitors, such as class I mannosidases at all. Thus, Treco et al. do not make up for the deficiencies of Friedman et al. and Smith et al." (page 17). These arguments are not persuasive because the Treco reference was used as teaching the production of GCB (gene-activated GCB) using HT1080 cells (claims 324, 332). It provides motivation to use human cells producing GA-GCB because they produce a greater amount of the desired protein. Arguments related to the Friedman et al. and Smith et al. references are discussed above.

The 112, 2nd paragraph rejection of claims 167-169 is withdrawn in view of the amendment.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

December 22, 2005